REMARKS

The Present Invention and the Pending Claims

The present invention pertains to citalopram hydrobromide with specific crystal properties and a method of crystallizing citalopram hydrobromide. Claims 21-37 are currently pending.

Summary of the Office Action

Claims 21-37 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of U.S. Patent No. 4,650,884 (Bogeso – H. Lundbeck A/S). Reconsideration of the pending claims is respectfully requested.

Discussion of the Obviousness Rejection

According to the Office Action, the Examiner contends that Bogeso discloses the inventive method and only differs by not mentioning that the cooling rate should be controlled. The Examiner also concedes that Bogeso does not disclose the particle size or the aspect ratio of the citalopram hydrobromide crystals. According to the Examiner, applicants must show the beneficial effect of controlling the cooling rate on the size of the citalopram crystals compared to the crystals obtained by Bogeso. In addition, the Examiner states that applicants also must demonstrate that the crystals obtained by the claimed method have superior properties and/or benefits compared to citalopram crystals previously prepared in the art.

The Examiner was not persuaded by applicants' previous response, which argued that the method disclosed by Bogeso is similar to that of Comparative Example 1 of the instant application. The Examiner, however, appears to have been confused by the nomenclature identifying the various examples in the specification of the present application. The specification contains a "*Reference* Example 1" (page 14, lines 8-20), "Example 1" (page 14, line 21, through page 15, line 13), and "*Comparative* Example 1" (page 18, lines 12-37). These are separate examples in the specification of the present application.

In particular, the Examiner states in the Office Action: "The applicants argue that the instant reference example 1 is similar to the first crystallization described by Bogeso" (page 2, lines 12-14). However, applicants have not made such an argument. Reference Example 1 is directed to a production method of *crude* citalopram hydrobromide, rather than to a production method of the citalopram crystal of the present invention (see page 14, lines

8-20, of the instant application). Applicants referred to *Comparative* Example 1, not Reference Example 1.

According to the Office Action, applicants allegedly have argued that "the instant comparative example 1 is similar to [the] third crystallization described by Bogeso" (page 2, lines 14-15). This statement also is inaccurate. The solvent, i.e., methanol/isopropyl alcohol, used in Comparative Example 1 (see page 18, lines 12-37, of the instant application) is the same as the solvents used for the *second* crystallization described in Bogeso (col. 5, lines 39-47) rather than the "third crystallization."

In addition, since the Office Action refers to the use of acetone by Bogeso (page 3, lines 5-7), it appears the Examiner has focused on the *third* recrystallization of Bogeso (col. 5, line 48, through col. 6, line 5). However, comparison of the third recrystallization with Comparative Example 1 of the instant application is meaningless because hexane also is used in the third recrystallization of Bogeso (col. 5, line 52). In view of this difference, *Comparative* Example 1 of the instant application and the *second* recrystallization of Bogeso (col. 5, lines 39-47) should be compared. These two methods are the same in that crude citalopram hydrobromide is completely dissolved in a solvent consisting of methanol and isopropyl alcohol and then recrystallized.

In the Office Action, the Examiner points out: "In the instant reference example 1 ... in contrast to the method of Bogeso" (page 2, line 17 through page 3, line 2). Again, applicants note that the method described in Reference Example 1 is a production method of *crude* citalopram hydrobromide. Reference Example 1 does *not* pertain to a method of crystallizing citalopram.

In the Office Action, the Examiner states that "Bogeso teaches that the mixture in all three crystallization steps is left overnight for crystallization" (page 3, lines 13-14). However, according to the method of Bogeso, in every crystallization step, the solution is "left overnight for crystallization" *after cooling to 20 °C* (col. 5, line 34, through col. 6, line 5). It is improper to ignore the step of cooling to 20 °C. As stated previously, it is believed that crystals in Bogeso's method start to precipitate out of solution *only* after being cooled to 20 °C in any of the three recrystallization steps. This belief is based on a similar step in *Comparative* Example 1 of the instant application.

In Comparative Example 1, citalopram hydrobromide crystals precipitated out of solution *only* after cooling the solution to 20 °C and the addition of a seed crystal (page 18, lines 12-37). As shown in the micrograph of the crystals obtained in Comparative Example 1 (see Figure 16), the aspect ratio of the resulting citalopram hydrobromide crystals is approximately 1. Since Bogeso teaches a similar method, the crystals obtained by the recited

method of Bogeso also would be reasonably expected to have an aspect ratio of approximately 1. As such, Bogeso does not teach or suggest preparing a citalopram hydrobromide crystal with an average aspect ratio of not less than 2.0 and not more than 9.0, as recited in pending claims 21-27.

Regarding method claims 28-37, as conceded by the Examiner, Bogeso does not disclose cooling the citalopram hydrobromide to allow for crystallization while controlling the cooling rate. Controlling the cooling rate is important in obtaining citalopram hydrobromide crystals of the present invention.

As explained above, Bogeso does not teach or suggest an average aspect ratio of not less than 2.0 and not more than 9.0, as required by claims 21-27. Moreover, the Examiner concedes that Bogeso does not disclose cooling the citalopram hydrobromide to allow for crystallization while controlling the cooling rate, as required by method claims 28-37.

Contrary to the Examiner's contention, applicants have already shown the beneficial effects of controlling the cooling rate and the unexpected superior activity of the crystals obtained by the claimed method. The claimed citalopram hydrobromide crystals can improve production problems "such as poor filtering performance after crystallization for the preparation of a pharmaceutical bulk and poor fluidity when crystals are being taken out" (see the specification at, for example, page 12, line 32, through page 13, line 3). In other words, the present inventive crystals with the claimed aspect ratio have simultaneously solved the problems of filtering performance and fluidity. Controlling the cooling rate, as recited in the production method of claims 28-37, provides citalopram crystals of the present invention. Bogeso does not appreciate any benefits of providing a citalopram hydrobromide crystal with an average aspect ratio of not less than 2.0 and not more than 9.0 nor teach how to provide such crystals. Since Bogeso does not recognize any of these surprising and unexpected benefits, one of ordinary skill in the art would not be motivated, nor know how, to alter the disclosure of Bogeso in such a way so as to arrive at the invention of claims 21-37.

In view of the foregoing, the present invention is not obvious in view of Bogeso, and applicants request that the obviousness rejection be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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